REMARKS/ARGUMENTS

Reconsideration of the present application in view of the following remarks is requested respectfully.

Claims 25 and 27 to 32 are pending. No claims have been amended, added or canceled.

Applicants acknowledge, with appreciation, the Examiner's favorable withdrawal of the previous rejections under Section 112 and for obviousness-type double patenting.

Discussion of the Office Action

All of the pending claims (Claims 25 and 27 to 32) have been rejected under 35 U.S.C. § 103 as being unpatentable over Dooley et al., U.S. Patent No. 5,610,271 ("Dooley") in view of of Lawhorn et al., *Anesthesia and Analgesia*, Vol. 72(1), pp. 53-57 (Jan. 1991) ("Lawhorn"), Ito, WO 96/06078 ("Ito") or Chang et al.,*J. Med. Chem.*, Vol. 37, pp. 4490-4498 (1994) ("Chang"). Applicants respectfully traverse the rejection.

Prima facie Obviousness Has Not Been Established

As the Examiner is aware, the Patent Office has the initial burden under Section 103 of establishing a *prima facie* case of obviousness. *In re Piasecki*, 223 U.S.P.Q. 785, 787 (Fed. Cir. 1984). This burden may be satisfied only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Applicants respectfully submit that this showing has not been made and, accordingly, the burden of establishing*prima facie* obviousness has not been met.

Independent Claim 25, which is the only pending independent claim, defines a method of treating or preventing pruritus in a mammal. The defined methods comprise the administration to the mammal of a kappa opiate receptor agonist. The claims further define that the kappa opiate receptor agonist is a non-peptide arylacetamide which is devoid of central nervous system effects. It is submitted respectfully that there is no disclosure or suggestion in the cited prior art, alone or in any proper combination, of the methods defined in independent Claim 25 and the claims dependent thereon.

In this regard, Dooley is directed to peptides which are said to be selective for the κ receptor (column 1, lines 63 to 64; abstract). Dooley fails completely to disclose or suggest methods involving the use of kappa opiate receptor agonists which are not peptides. Clearly, Dooley is utterly devoid of any teachings regarding kappa opiate receptor agonists in the form of arylacetamides.

The Examiner has acknowledged in the Office Action that applicants' claims define over Dooley since this patent is limited to peptides. In an effort to cure these deficiencies, Dooley has been combined with various secondary references. These secondary references are apparently cited for, *inter alia*, their disclosure of phenylacetamide compounds. Applicants respectfully submit that this rejection is improper, in the first instance, since the appropriate standard for establishing *prima facie* obviousness has not been applied. Accordingly, it is respectfully submitted that the rejection based on the combined teachings of Dooley and the secondary references is improper and should be withdrawn.

The Standard for Establishing *Prima Facie* Obviousness

It is well settled that it is improper to pick and choose from any reference so much of it as will support a given position, without considering the teachings of the reference as a

whole. *In re Wesslau*, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965). Nevertheless, it is respectfully believed that this is what has occurred here. Isolated disclosures of certain methods involving peptide compositions have been selectively extracted from Dooley, and isolated disclosures of methods involving compounds which display κ receptor agonist activity and isolated disclosures of phenylacetamide compounds have been selectively extracted from the secondary references. These isolated disclosures were then combined, absent a teaching in the art or a convincing line of reasoning for doing so, in an effort to arrive at applicants' invention.

With regard to the teachings of the secondary references, Lawhorn is directed to a study on the combined administration of morphine and butorphanol[1] to patients undergoing epidural anesthesia for cesarean delivery. *See* abstract. Independent Claim 25 distinguishes over Lawhorn in that (1) butorphanol is not an arylacetamide and (2) butorphanol is a centrally acting narcotic. *See, e.g., Physician's Desk Reference*, 46th Edition, pp. 721-722 (1992). Moreover, as set forth in Lawhorn, butorphanol is a mixed μ receptor antagonist and κ receptor agonist. Lawhorn is utterly silent as to whether butorphanol is responsible for the relief of pruritus and, if so responsible, whether this is due to butorphanol's activity as a μ receptor antagonist or κ receptor agonist, or some combination of these activities.

Ito is directed to N-(2-(pyrrolidinyl-1)-1-phenethylacetamides and their use as analgesics, antiinflammatories, diuretics or neuroprotective agents (page 1, lines 1 to 7). Chang is directed to benzeneacetamides and their activity as κ selective agonists and/or antagonists (abstract). There is no disclosure or suggestion whatsoever in Ito or Chang regarding the use of the disclosed compounds for the prevention or treatment of pruritus. Nor

1 The chemical name of butorphanol is N-cyclobutylmethyl-3,14-dihydroxymorphinan.

do Ito or Chang teach that the disclosed compounds are devoid of central nervous system effects.

Thus, nowhere in any of the cited references is there a disclosure of methods for the prevention/treatment of pruritus as defined in applicants' claims, which methods comprise the administration to a mammal of an arylacetamide, non-peptide kappa opiate receptor agonist that is devoid of central nervous system effects. Moreover, it is respectfully submitted that there is absolutely no disclosure or suggestion in the cited art which would motivate the skilled artisan to modify Dooley, for example, by substituting Dooley's peptides with phenylacetamide compounds as described in Ito and/or Chang. The law is abundantly clear that in the absence of such a disclosure or suggestion, there is inadequate support for an assertion by the Patent Office that this modification would *prima facie* have been obvious. *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989) ("[t]hemere fact that the prior art could be so modified would not have made the modification obvious *unless the prior art suggested the desirability of the modification*"), *quoting In re Gordon*, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (emphasis added). In the absence of a disclosure in the art or a convincing line of reasoning which suggests the modification, the obviousness standard upon which a rejection is based is the "obvious to try" standard. This is not an appropriate standard -- the art must suggest with some degree of certainty the success of that which applicants are claiming as their invention. *In re Dow Chem.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); and *In re Tomlinson*, 150 U.S.P.Q. 623 (C.C.P.A. 1966).

In rejecting applicants' claims, the following statement appears in the Office Action.

> Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed [the; sic] invention was made, to employ the arylacetamide kappa opioid receptor agonist known in the art as disclosed [in Ito] or Chang et al. for treatment of pruritis because kappa opioid receptor agonists are known to be useful in suppressing the pruritis.

See Office Action, page 3. The cases of *In re Boesch*, 205 U.S.P.Q. 215 (CCPA 1980) and *Ex parte Winters*, 11 U.S.P.Q.2d (Bd. Pat. App. & Int. 1989) are cited in the Office Action as further supporting the rejection. For the reasons discussed in detail above, applicants disagree respectfully with the statement that the claimed methods would have been within the skill of the ordinary artisan. Applicants also submit respectfully that the *Boesch* and *Winters* cases have been cited out of context, and that they are inapplicable in the present situation.

In this connection, the applicant in *Boesch* claimed alloys composed of ranges of constituents, as well as a maximum "N_v" (*i.e.*, average electron vacancy concentration per atom in the alloy's matrix). The prior art taught alloys whose constituent ranges overlapped with the claimed constituent ranges. The prior art also taught the desirability of modifying the N_v of prior art alloys to obtain applicant's claimed N_v. Based on these teachings, the Court ruled that a *prima facie* case of obviousness was established since the prior art "suggested the kind of experimentation necessary to achieve the claimed composition". *Boesch*, 205 U.S.P.Q. at 219.

In *Winters*, the applicant claimed a subgenus of compounds falling within a broader genus. Relevant to the present case is the ruling that under these circumstances, the *Winters* Examiner made out a *prima facie* case of obviousness, and that any objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support. *Winters*, 11 U.S.P.Q.2d at 1388.

Applicants submit respectfully that *Boesch* and *Winters* are inapplicable to the present rejection in that the cited prior art simply does not provide any teachings, specifically or generically, which would provide a suggestion that the administration of non-peptide arylacetamide kappa agonist compounds that are devoid of central nervous system effects

may be useful in the prevention or treatment of pruritus. Clearly, the present situation does not involve overlapping ranges or genera (as in *Boesch*) or a selection of a subgenus within a larger genus (as in *Winters*).

In addition to being inapplicable to the present situation, it is submitted respectfully that *Boesch* has been cited out of context. In this connection, in ruling that the prior art suggested the kind of experimentation necessary to arrive at the claimed composition, the *Boesch* court held the following.

> This accords with the rule that discovery of an optimum value of a result effective variable in a ***known*** process is ordinarily within the skill of the art.

In re Boesch, 205 U.S.P.Q. 215, 219 (C.C.P.A. 1980) (emphasis added). Thus, according to the *Boesch* court, it is *prima facie* obvious when a patent applicant claims an optimized value of a result effective variable in methods which are disclosed in the prior art. This is not the case here. Applicants' claims define methods of preventing and treating pruritus which involve the administration of non-peptide arylacetamide kappa agonist compounds devoid of central nervous system effects. As discussed in detail above, the cited art fails completely to disclose or suggest these claimed methods.

In view of the foregoing discussion, reconsideration and withdrawal of the rejection under Section 103 are requested respectfully.

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